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Experimental Method for Microbubbles Dynamics Monitoring and Radius Sizing

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Abstract

Rationale and aim: Within the context of divers' decompression illness prevention, ultrasonic detection and sizing of circulating microbubbles in blood is of great interest. In order to be representative of the divers gas tension level (supersaturation) and thus, to optimize decompression stages, the measurements (made in the right ventricle region) should be performed during a short period of time (ventricle filling <20 ms), efficient to detect a broad range of bubbles' radii population (radius from 20 to 200 _m) and harmless (Mechanical Index MI<0.3).
Materials and methods: Based on a bi-frequency ultrasound excitation, the purpose of our method is to measure the relative and the absolute microbubble size variations. Because of our research interests, the experimental investigations were conducted on natural microbubbles, with radius ranging between 20 and 200 µm, excited around their resonance frequencies by a low frequency transducer. Different types of excitation were tested (sweep, burst, pulse). A pair of high frequency transducers were arranged to focus at a common point. One of the transducers was used to transmit a 2ms duration high-frequency (1 MHz) pulse while the other was used to passively receive backscattered signals. The scattered signal was acquired and visualized on a digital oscilloscope and transferred for offline calculations. Signal treatment were conducted in order to recover the amplitude and frequency modulations.
Results: Using the same experimental setup, simple signal processing applied on both the amplitude and the frequency modulations leads to a double characterization of the microbubble dynamics. Moreover, under the assumption of small radial oscillations, the equilibrium radius of the microbubble can be accurately estimated.

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Keywords: Microbubbles; Sizing

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1. Introduction

In the context of divers desaturation accident prevention, ultrasonic detection and sizing of circulating microbubbles in blood is of interest but had to fulfill power, duration and technical requirements. The classical dual frequency methods, based on the detection of the resonance frequency (Chapelon et al, 1985), present severe limitations for this task, since the frequency range covered by the excitation signals needs to encompass the resonance frequency. Moreover because the transducer bandwidths are always limited, the range of microbubble size that could be measured is therefore limited. Extension of the investigation range has been proposed, using non-linear excitation (Fouan et al, 2014) but the method is still restricted to resonance frequency detection.

In this work, an extension of the “acoustical camera” principle (Renaud et al, 2012a) is proposed. This technic is also based on a dual frequency excitation but it includes an analysis of the amplitude modulation that allows a characterization of the relative radius variations. This method has been applied with various excitations (Renaud et al, 2012b) and in different situations (Renaud et al, 2014). The purpose of the present work is to jointly analyze the amplitude modulation and the frequency modulation induced by the bubble oscillations.

2. Materials and Method

2.1. Amplitude and frequency modulation

The method is based on a dual frequency excitation of the microbubble. The microbubble is excited by a low frequency (LF) wave near its resonance frequency and is detected by a high frequency (HF) wave. As proposed by Renaud (Renaud et al, 2012a), the relative variations of the backscattered signal amplitude ($\Delta A/A_0$) are linked to the relative variations of the microbubble radii ($\Delta R/R_0$).

$$\frac{\Delta R}{R_0} = \frac{\Delta A}{A_0}, \tag{1}$$

where R_0 is the equilibrium radius of the bubble and ΔR the radius variation. In the radial motion approximation, each time the wall of the microbubble is moving, a frequency modulation is induced and a Doppler effect is perceptible on the measurement. The radial velocity of the bubble’s wall (v) is connected to a shift in frequency (Δf) and the radius variation ΔR has therefore a definite relation with both the phase shift $\Delta\varphi$ and the incident angle θ of the HF wave:

$$v = \frac{c}{2f\cos(\theta)}\Delta f, \tag{2}$$

$$\Delta R = \frac{c}{4\pi f\cos(\theta)}\Delta\varphi, \tag{3}$$

Therefore, a combined measure of the amplitude and phase variations in the backscattered signal should allow an estimation of the relative and absolute variations of the microbubble radius under the LF excitation.

2.2. Experimental setup

The experiments were performed in a 2 m x 3 m x 0.5 m water tank in order to reduce the effects of any standing waves resulting from the multiple reflections at the boundaries. A hydrojet (Braun OralB) was used to generate microbubbles (radii ranging from 20 µm to 200 µm). A thin wire was placed on the path of the rising bubbles, and measurements were performed on a single tethered bubble. Using this simple method, several measurements were carried out under the same conditions and then compared to each other. The micro-bubble radius was assumed to be constant during the 2 ms-duration of the measurement (Fyrillas, 2006), including 1 ms of LF excitation. The acoustically characterized bubbles were optically monitored at the same time by a CCD camera. The acoustic measurements were performed using three confocused transducers. The first transducer radiated the LF pumping wave (Ultran, GMP 50 kHz, Hoboken, New Jersey, USA), at 5 kPa and with a chirp in frequency increasing from 30 to 60 kHz. The other two were used for the transmission and reception of the imaging wave (Imasonic, 1 MHz; f = 90 mm, Besançon, France) at 10 kPa and 1 MHz. Regarding our research interests (decompression sickness prevention), the pressure amplitudes has to be limited, especially at low frequencies, to avoid cavitation and biological damages in gas saturated tissues. Furthermore, as explain by Renaud (2012a), the amplitude of the probing wave should be low enough in order to remain in the (quasi-)linear regime. The two emitting transducers were connected to an arbitrary waveform generator (LeCroy, ArbStudio 1104, four channels, Thousand Oaks, California, USA). The backscattered signal is recorded by an oscilloscope (Agilent Technologies, Infini-iVision DSO5014A, 100 MHz, Santa Clara, California, USA).

For both phase and amplitude estimations, as suggested by Renaud et al. (2012a), we make use of short sliding time windows on the backscattered HF signals. For each time window, the amplitude is evaluated at 1MHz in the frequency domain. At each time, the relative radius variation is determined by Eq.1. The phase is estimated and then, knowing the HF frequency and the angle between the two HF transducers, the absolute variation ΔR is calculated using Eq.3. The time windows should be set between the LF and the HF periods. A 6 µs window length has been chosen and a 0.2 µs step is applied between two consecutive windows. These parameters allow a 5 MHz final sampling for the bubble variation curves.

3. Experimental evidence

An example, with a 69 µm radii bubble, of the double modulation extraction is shown on Figure 2. Relative (Fig. 2.a) and absolute (Fig. 2.b) radius variations are plotted during time. On both curves, the three part of the measurement are clearly identifiable. From 0 to 0.45 ms, there is no LF excitation, only HF detection. As it is visible, there are no amplitude nor frequency modulation. Then the LF excitation is turned on and both modulation are measurable. Finally, as in the beginning, the excitation is off and only remaining signals are measured (due to reflections in the water tank essentially. During excitation, these two curves show similar trend in amplitude and phase. Their comparison gives valuable information about the microbubble characteristics.

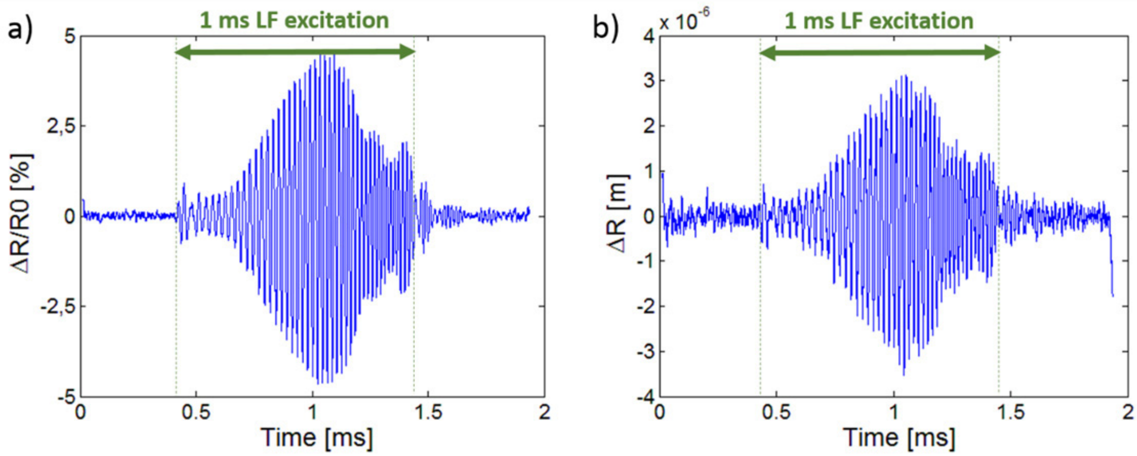

Fig. 1. Measurement of the relative (a) and of the absolute (b) radius variations of a 69 µm radius bubble excited by a chirp (30-60 kHz) at 5 kPa.

4. Discussion

A resonance is clearly identified for both curves. The resonance frequency can be estimated using the instantaneous driving frequency and the corresponding resonant radius calculated (with Minnaert frequency). Regarding the pressure levels and the microbubble size, the Minnaert formula should be precise enough. Two resonant radius are estimated at 69.5 and 68.8 µm. These radius are comparable to the optical radius measured at 69 µm (the CCD camera optical resolution is 2.3 µm). The amplitude resonance is attenuated by the very short chirp used (1 ms).

As said before, the two curves are comparable. To be accurate, the two measures does not correspond to the exact same variations. The relative radius variations, as it comes from the amplitude modulation, correspond to the change in size of the microbubble, in the orthogonal direction of the HF propagation (bubble cross-section). On the other hand, the absolute variations correspond to the change in size in the direction of the HF propagation (Doppler effect). But as it is described in most of the theoretical models, only the changes in volume are considered (especially at very low pressure levels (Ainslie and Leighton, 2011)). This means that the two variations measured are supposed equivalent, or in other words, that the bubble shape remains asymmetrical. Therefore the ratio between the absolute and the relative variations constitutes an estimator of the equilibrium radius. In order to prevent any phase shift, due for example to the presence of the wire, only the modulus of the radius variation is assumed to be constant. The modulus ratio is shown on Figure 3. Firstly, when the power is off, the ratio is insignificant, because the bubble is not oscillating. Secondly, when the bubble is excited, the ratio is almost constant. Finally, after the excitation duration, the ratio again becomes meaningless. The averaged ratio over the acoustic excitation time provides a value of 67.2 µm that is closed to the equilibrium radius measured with the camera.

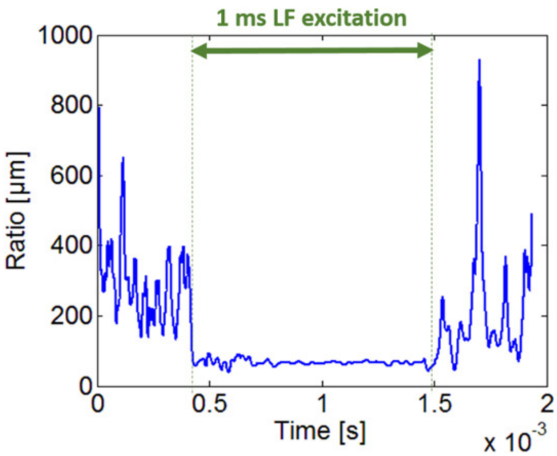

Fig. 3. Bubble radius estimation: Ratio between the absolute and relative radius variations curves (Fig. 2.b and 2.a) of a 69 µm radius bubble excited by a chirp (30-60 kHz) at 5 kPa.

4. Conclusion

The method presented in this paper is a noticeable improvement in the field of microbubble sizing. The method proposed here had a noticeable advantage against classical dual frequency method, because it does not need to encompass the resonance frequency of the bubble. Indeed, the estimation of the bubble radius given in Figure 3 is relevant before and after the resonance. Therefore, any excitation waveform, sufficient to make the microbubble oscillate could be used. Chirps, burst and short pulses have been tested and validated (Fouan et al, 2015). It has been shown, with an *in-vitro* setup, that small LF amplitude (<5kPa) is sufficient to detect amplitude and frequency modulations and hence to determine accurately the equilibrium radius of the microbubble. Because the main requirements have been successfully achieved, an adaptation of an existing 2 MHz Doppler system with a carefully chosen excitation is under study for in vivo application.

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